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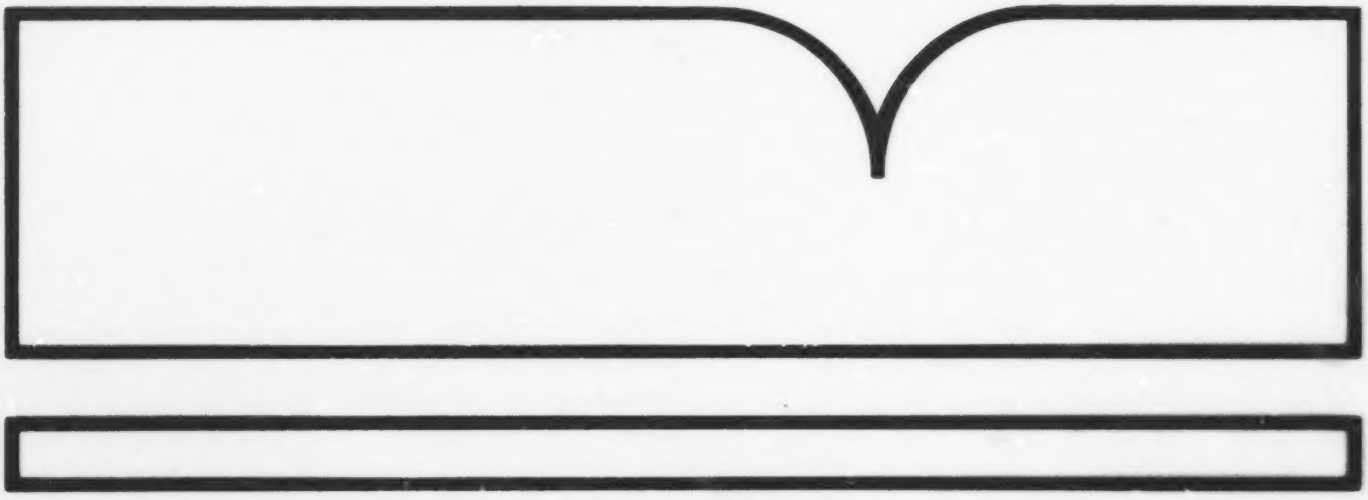

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CRITICAL ISSUES IN INTRA- AND INTERSPECIES DOSIMETRY OF OZONE

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ABSTRACT

Knowledge of dose at the target site is a fundamental starting point in making interspecies dosimetric comparisons. To the extent that information is available on the effective dose of a compound, our confidence in risk assessments is increased. To facilitate judgments about effects determined in animals relative to likelihood of risk associated with human exposure to ozone (O_3), a mathematical dosimetry model has been developed for interspecies comparisons. The model incorporates the major factors affecting the absorption of O_3 in the respiratory tract: the morphology of the respiratory tract, the route, depth and rate of breathing, physicochemical properties of O_3, the physical and chemical processes which govern gas transport, and the physicochemical properties of the lining fluids and tissue material of the airways and gas exchange units. This model is used to identify issues critically important to the modeling process itself, such as model validation and modeling uptake of O_3 in the head. Also discussed are the application of the dosimetry model for examining age-dependent susceptibility to O_3 and the potential usefulness of such models for relating microdosimetry to microtoxicology.

INTRODUCTION

Ozone is a ubiquitous air pollutant. In the United States, millions of people are exposed to O_3 levels that exceed the current National Ambient Air Quality Standard (NAAQS) of 0.12 ppm for one hour, not to be exceeded more than once per year. Recently, the need for an eight-hour O_3 standard has been advocated since large segments of the population may be routinely exposed for extended periods to O_3 levels just below those of the current 1-hour standard (ref. 1). The rationale for such a recommendation is based mainly upon: 1) well-documented biochemical and functional effects in laboratory animals and man associated with brief exposures to O_3 (ref. 2), and 2) a concern that long-term exposure to elevated O_3 levels may possibly lead to the development of chronic lung diseases. While various morphologic and

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histopathologic changes have been observed in animals exposed subchronically and chronically to O_3 (ref. 2, 3, 4), whether such changes lead to irreversible disease has not yet been established. Among the fields of epidemiology, human clinical studies, and animal toxicology, animal studies can provide the most complete data on the array of effects associated with chronic exposure.

Mathematical models have been developed (ref. 5, 6) for use in interspecies comparisons of dose when assessing the relevance and implication of results from animal studies for the likelihood of similar effects occurring at O_3 levels to which humans are exposed. While advances have been made in our understanding of the respiratory tract dosimetry of O_3, various topics relative to the models per se, to the input data required by the models, and to model application must be addressed in light of the increased utilization of these models to make intra- and interspecies dosimetric comparisons. A discussion of some of these topics is the intent of this paper.

DOSIMETRY MODEL: FORMULATION AND COMPUTER SIMULATION

Detailed descriptions are available elsewhere (ref. 5, 6, 7) of the O_3 dosimetry model used in this paper. Here, a brief description of the model formulations and the computer simulation program is provided to inform the reader of the nature of the dosimetry model and applications of it.

Major factors affecting the uptake of O_3 are the morphology of the respiratory tract, the route, depth, and rate of breathing, physicochemical properties of O_3, the physical processes governing gas transport, and the physicochemical properties of the respiratory tract lining fluids and tissue of the airways and gas exchange units. The complex interaction of these factors determines the dose delivered to target sites within the respiratory tract. Although it is desirable to consider as many as possible of the above factors in developing a simulation model, simplifying assumptions and structures are often required to make the modeling problem tractable.

Species lung dimensions are taken into account using anatomical or airway models such as those available for the rat (ref. 8) and for man (ref. 9). In these models, lower respiratory tract (LRT) airways are characterized by a sequence of sets of right circular cylinders. If the upper respiratory tract (URT) region is included, it consists of pretracheal "generations" or sequential segments. Data on the number of airways or segments and their diameters and lengths are needed for each generation or segment in the model respiratory tract. Also, estimates of alveolar volumes and surface areas must be available for the pulmonary region, while surface area and volume estimates are needed for URT segments.

Given the O_3 concentration at the first model segment (e.g., nose, mouth, or trachea), the model simulates the transport and absorption of O_3 in each airway and alveolar space of the anatomical model during one or more breaths. During the simulated breathing cycle, changes in lung volume are accounted for by isotropically varying the linear dimensions of the LRT airway generations. Volume flow rates can be simulated during breathing based either upon experimental data or upon an assumed time-dependent function.

Gas transport in the lumen and air spaces, as well as chemical reactions and transport in the liquid lining, tissue, and blood compartments, is taken into account in the simulation model via partial differential equations. The complex series of reactions of O_3 with various biological constituents is simplified to one reaction involving an effective second-order rate constant and the overall constant concentration of chemical components (resulting in a pseudo first order reaction) that react with O_3. Given initial and boundary conditions, in addition to values for the physical, chemical, and biological parameters of the model, the solutions of the equations provide predicted O_3 doses for each model compartment in any given anatomical generation. Consequently, respiratory tract patterns can be compared among various animal species and man for specified O_3 concentrations.

CRITICAL ISSUES

Model Validation

The usefulness of dosimetry models to risk assessment and extrapolation modeling depends to a large extent on the degree to which model predictions agree with the results of experiments. Until recently there was very little experimental data available for O_3; however, techniques have been and are being developed to measure the uptake and distribution of O_3 in the respiratory tract of humans and animals (ref. 10, 11). The data of Wiester et al (ref. 10) for rats and of Gerrity et al. (ref. 11) for humans characterize the total uptake and the URT and LRT uptakes of O_3, respectively. However, these data are insufficient to infer the distribution of absorbed O_3 within the tracheobroncial (TB) and pulmonary regions of the LRT. Position emission tomography and isotope ratio mass spectroscopy are experimental methodologies that may allow the determination of the distribution of absorbed O_3 in specified regions of animals and humans. The results of all these experimental approaches will allow for the refinement of the values of the physiological parameters used in dosimetry models, resulting in more accurate predictions and an increased confidence in dosimetry model results.

Accounting for O_3 Loss in the URT

Because the URT can remove as much as forty percent (ref. 11) and possibly more of O_3 from inspired air, this region plays a major role in the dose of O_3 delivered to different locations in the LRT. The major effect of the URT is to reduce the quantity of O_3 that penetrates to the LRT; however, the effect on the relative distribution of absorbed O_3 is probably minor (ref. 12). Modeling uptake in the LRT by only specifying an empirically derived concentration at the tracheal entrance can lead to large errors in predicted LRT dose, depending on species and magnitude of URT removal (ref. 12). Thus, a complete respiratory tract model that accurately predicts URT uptake for a wide range of ventilatory parameters and species is necessary. One way to account for URT removal is to use a simple chamber that removes the appropriate quantity of O_3 (determined by experiments) in the animal species being modeled. At the other extreme, validated mathematical models that take into account the complex URT anatomy and physiological processes of O_3 removal could be used. In either case, experiments conducted specifically to characterize uptake by the URT of laboratory animals and humans are critically needed.

Age Susceptibility to Ozone

In 1974, Bartlett and coworkers (ref. 13) suggested that young animals have an increased sensitivity to O_3, although the experimental design of their studies did not really provide the appropriate framework for such an inference. Biochemical changes in the lung have been more readily observed in neonatal and young animals than in older animals (ref. 14,15). On the other hand, postnatal rats are resistant to O_3 exposure until weaning (ref. 16). In studies comparing the effects of 0.12 ppm and 0.25 ppm O_3 on the proximal alveolar region of juvenile and adult rats, Barry et al. (ref. 3) found no statistically significant age-dependent effects on a multitude of morphometric measures of volume, surface area, and densities of cells and other tissue components. However, effects indicative of epithelial injury were attributable to O_3 even at the 0.12 ppm exposure level in both juvenile and adult rats.

In humans, there is evidence from epidemiological and field studies that exercising children and adolescents may experience decrements in pulmonary function when exposed to ambient levels of O_3 below the present NAAQS of 0.12 ppm during normal activities (ref. 17,18). However, exposures of adults for two hours with intermittent heavy exercise to 0.1 ppm O_3 does not alter pulmonary function (ref. 19).

While the above studies would appear to support an assertion that children are more sensitive to O_3 than adults, the studies do not provide a definitive answer since both groups were not examined under comparable conditions. To date, only McDonnell and coworkers (ref. 20) have compared the effects of O_3 exposure on the pulmonary function of children and non-smoking adults, normalizing the exercise for body size to yield a minute ventilation (V_E) of approximately 35 liters per min per square meter of body surface area.

Demographic, descriptive statistical, and respiratory function data from the McDonnell et al. (ref. 20) study are given in Table 1. With respect to the typically reported measurements of forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), there appears to be a similarity in response to 0.12 ppm O_3 between children and adults for levels of exercise yielding comparable V_E normalized for body surface area (BSA). However, with respect to the reporting of cough as a symptom associated with the O_3 exposure, adults experienced a significant increase ($p<0.005$) while children did not ($p=0.16$). As McDonnell et al. (ref. 20) note, children appear to be less responsive to O_3 regarding the induction of cough.

TABLE 1

A comparison of the effects of 0.12 ppm O_3 in children and adults[a]

	Children			Adults		
Age (yrs)	9.9			22.5		
Height (cm)	141			180		
	Air	Ozone	P	Air	Ozone	P
Heart rate (beats/min)	158 ± 13	158 ± 15		166 ± 10	163 ± 12	
V_E (l/min)	38.2 ± 6.2	39.4 ± 7.4		66.2 ± 7.6	68.0 ± 7.4	
V_E/BSA (l/min/m^2)	32.4 ± 3.3	33.3 ± 3.4		34.9 ± 3.1	34.3 ± 2.9	
FVC (%)	-0.1 ± 0.7	-1.8 ± 0.7	0.08	-0.9 ± 0.4	-3.1 ± 1.1	0.04
FEV_1 (%)	-0.5 ± 1.1	-3.4 ± 1.1	0.03	-1.1 ± 0.5	-4.3 ± 1.1	0.02
Cough	0.0 ± 0.1	0.1 ± 0.2	0.16	0.1 ± 0.0	0.8 ± 0.2	<0.005

[a]This table was constructed from Tables 2 and 3 of McDonnell et al. (ref. 20). Sample sizes vary between 17 and 23 for the entries in the table. Significance probabilities (P) for children were determined using paired t-tests and for adults using non-parametric Williams' tests.

How do dosimetry modeling predictions of O_3 dose compare for the ages and exercise levels used by McDonnell et al. (ref. 20)? Overton and Graham (ref. 21) utilized several sources of data on age-dependent LRT volumes, age-dependent airway dimensions, an adult tracheobronchial region model, and a model of the adult pulmonary acinus to construct theoretical LRT lung models

model (ref. 5, 6) to estimate dose patterns in the various anatomical models. Using the same procedure and dosimetry model, we have simulated the absorption of O_3 in children and adults not only with the average ages and ventilatory parameters that correspond to the subjects in the McDonnell et al (ref. 20) investigation, but also for these ages undergoing quiet breathing.

In Figure 1A, the LRT dose patterns for doses from the trachea to the most distal alveoli are shown for the 9.9 and 22.5 year olds during quiet breathing and for heavy exercise with V_E equal to that given by McDonnell et al. (ref. 20) for the two age groups. Figure 1B, from reference 21, illustrates dose patterns for two "extreme" ages (birth and adult) and

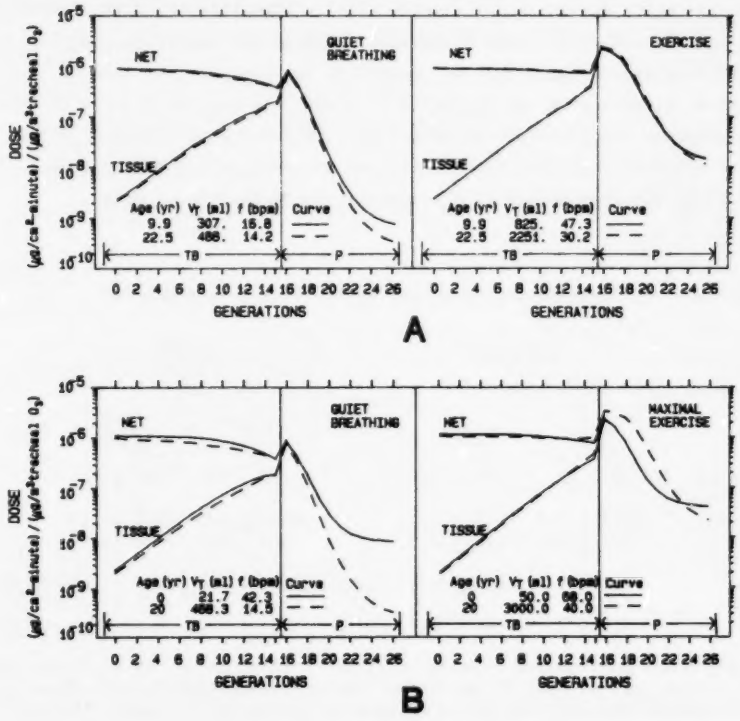

Fig. 1. Net and tissue dose versus generation. The figures illustrate the effect of several breathing states and different ages on the distribution of absorbed ozone in the respiratory tract of humans, given that the tracheal ozone concentrations are equal. TB and P indicate tracheobronchial region and pulmonary region, respectively. Fig. 1A. Ventilatory parameters and ages based on McDonnell et al. (ref. 20). Fig. 1B. "Extreme" age and ventilatory parameters used (based on ref. 21, with permission).

breathing states (quiet and maximal breathing). Both net (the total O_3 removed in the liquid lining, tissue, and blood) and tissue dose curves are depicted in the figures. The definition of dose is the quantity of O_3 absorbed per minute per unit area for a given generation and compartment(s) divided by the ambient O_3 concentration. Only the tissue dose is depicted for the pulmonary region because, here, tissue dose is essentially equivalent to net dose, differing by a few percent due to absorption of O_3 in the blood and negligibly in the liquid lining.

According to Fig. 1A., the LRT dose patterns for quiet breathing and for heavy exercise (V_E normalized to body surface area) are essentially the same for the 10 and 22 yr old. Fig. 1B contrasts LRT dose patterns for the infant compared to the adult for quiet breathing and maximal exercise. The TB doses are independent of age; however, major differences in tissue dose occur in the pulmonary region as a function of age and level of activity. With quiet breathing the infant receives, on the average, a significantly greater pulmonary tissue dose of O_3 than does the adult. Although not depicted in Fig. 1B, the pulmonary dose curves for other ages between infant and adult generally fall between the two quiet breathing curves with dose per generation decreasing with increasing age (ref. 21). In contrast to quiet breathing, at maximal work most pulmonary generations in the adult lung receive a greater delivered dose of O_3 compared to the infant. In the first to the middle portion of the pulmonary generations dose increases with age; between the 22nd and 24th generations the age-specific curves cross so that dose decreases as age increases.

In view of the above, it is apparent that if pulmonary function changes (FVC, FEV_1) are mediated through receptors in the TB or in the pulmonary region, then, based on McDonnell et al. (ref. 20) and from a dosimetric viewpoint, children and adults should be equally sensitive to O_3 during exercise in which their V_E's, normalized to body surface area, are equal. However, since very young (preschool) children exposed during normal respiration or light activity are likely to receive greater pulmonary doses of O_3 than adults, the potential for effects on the pulmonary function of these children may be greater. It should be noted that the possible validity of the above inferences are limited to assumption of upper respiratory tract removal of O_3, mucous composition, mucus thickness, etc. being the same in children and adults.

Microdosimetry of O_3 for Toxicological Assessments

In the context of this section, microdosimetry refers to estimating the O_3 dose to more localized areas within the lung such as a specific pulmonary

acinus or along a given path from the trachea. The critical importance of validating mathematical dosimetry models was discussed earlier. Obviously, the more complex the model and the more localized one wishes to predict dose, the more difficult it may be to obtain model validation. However, this should not act as a deterrant to validating models and to using them to examine localized dose and corresponding toxicological injury.

The potential value of microdosimetry for toxicological assessment is enormous, especially for evaluating the development or lack thereof of chronic lung disease associated with low level exposures to environmental pollutants. Although morphometric studies at the electron microscopic level are costly and labor intensive, they are requisite for establishing structural alterations and disease associated with environmentally relevant chronic exposure levels. An example of the type of morphometric data that has been obtained from O_3 exposure studies is given in Fig. 2, which shows the volume density of Type I epithelium in the proximal alveolar regions of control and O_3-exposed rats.

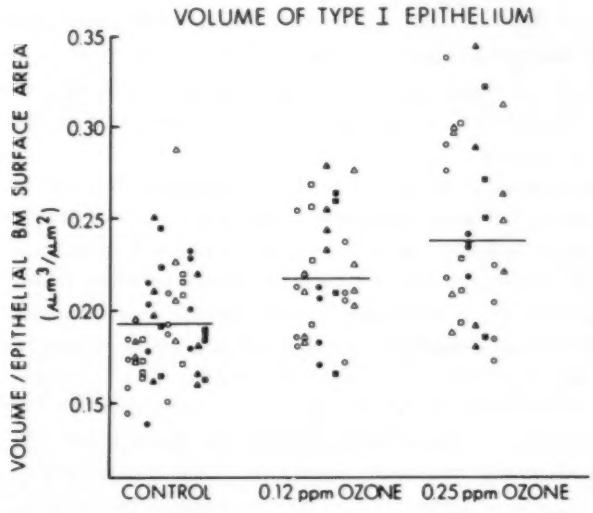

Fig. 2. Volume density of type 1 epithelium in the proximal alveolar regions of control and O_3-exposed rats. Each column of four identifical symbols represents the four data values calculated for this parameter for each animal. The horizontal bar in each symbol cluster represents the mean for the animals in that group. (Reproduced with permission from ref. 3.)

Could knowledge about localized distributions of O_3 dose within the respiratory tract impact, from both cost and design viewpoints, the use of morphometry to assess effects? To answer this question, let us first examine some aspects of dose patterns that may be relevant. Utilizing three-dimensional reconstruction techniques, Mercer and Crapo (ref. 22) determined the dead space volume to and the gas volume of 71 ventilatory units sharing a common branch point from the lobar bronchus of the left lung of a rat. A ventilatory unit is defined as a structure which includes all distal gas-exchange structures from a single bronchiolar-alveolar junction. Fig. 3 depicts a reconstruction with the bronchial alveolar junctions (darkened areas) shown at the end of the airways, along with the relative quantity of fresh air predicted to be delivered on inspiration to the ventilatory units distal to the junctions. While the majority of ventilatory units receive similar quantities of delivered fresh air, 3-fold greater than average quantities, as well as 3-fold less are possible. Analogously, when Overton et al. (ref. 23) modeled O_3 absorption in the rat along "longest" and "shortest" paths given by Raabe et al. (ref. 24), they found significantly different net dose profiles. While the maximum dose along each path occurs in the first alveolated duct, there is a 3-fold increase in net dose at this location for the "shortest" path as compared to the "longest" path.

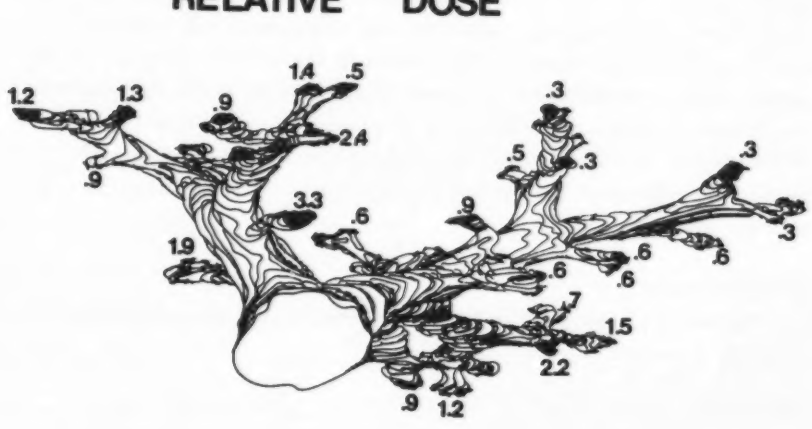

Fig. 3. Distribution of fresh inspired gas. The illustration is a representation of a three-dimensional reconstruction of airways off of a lobar bronchous. The figures on the diagram are the relative quantities of fresh air delivered to the ventilatory units on inspiration. The darked in areas indicate the junction between the ventilatory units and the airways. (Reproduced with permission from ref. 22).

The above kinds of analyses provide a plausible explanation as to why pathologists observe a patchy distribution of injury when examining slides cut randomly through parenchymal tissue. If the extent of O_3 variability in injury can be demonstrated to be due in large part to the path length from the trachea to the ventilatory unit, then it may be possible to take advantage of this fact in the following way. Morphometric analyses, such as illustrated by Fig. 2, could utilize reconstruction techniques so that exactly the same ventilatory unit locations could be examined in control and O_3 exposed animals. This could decrease the observed experimental variation in injury substantially, thereby requiring fewer animals to demonstrate statistical significance as well as yielding large cost savings. Moreover, by accounting for path distance, it follows that concentration-response data may be generated by comparing different ventilatory units within the same animal.

SUMMARY

This paper has discussed the role of dosimetry models in recognizing and assessing critical issues in intra- and interspecies dosimetry of ozone. As a background, the formulation of an ozone dosimetry model was outlined. Discussed next was the importance of model validation and the need for URT dosimetry models and experimental data on URT removal. Following this, two examples were given of the use of dosimetry modeling in conjunction with experimental results to gain a better understanding of toxicity and dosimetry. In the first example, results of the effect of O_3 on the pulmonary function of children and adults was discussed in the light of dosimetry model predictions of local doses in children and adults. In the second, model predictions of large variations of dose in the centriacinar region were discussed and compared to the observed large variations in morphological injury due to O_3; a method for reducing the variability in observed effects as well as for reducing the cost of morphological analyses was suggested.

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REFERENCES

1 P.J.A. Rombout, P.J. Lioy, and B.D. Goldstein, JAPCA, 36 (1986) 913-917.

2 U.S. Environmental Protection Agency, Air Quality Criteria for Ozone and Other Photochemical Oxidants, Vol. 4, EPA/600/8-84/020eF, Research Triangle Park, NC, 1986.

3 B.E. Barry, F.J. Miller, and J.D. Crapo, Lab. Invest., 53 (1985) 692-704.

4 B.E. Barry, R.E. Mercer, F.J. Miller, and J.D. Crapo, Exp. Lung Res., 14 (1988) 225-245.

5 F.J. Miller, J.H. Overton, Jr., R.H. Jaskot, and D.B. Menzel, Toxicol. Appl. Pharmacol., 79 (1985) 11-27.

6 J.H. Overton, R.C. Graham, and F.J. Miller, Toxicol. Appl. Pharmacol., 88 (1987) 418-432.

7 F.J. Miller, J.H. Overton, Jr., E.D. Smolko, R.C. Graham, and D.B. Menzel, In Pharmacokinetics in Risk Assessment/Drinking Water and Health, National Academy Press, Vol. 8, Washington, DC, 1987, pp 353-368.

8 H.C. Yeh, G.M. Schum, and M.T. Duggan, Anat. Rec., 195 (1979) 483-492.

9 E.R. Weibel, Morphometry of the Human Lung, Academic Press, New York, 1963.

10 M.J. Wiester, T.B. Williams, M.E. King, M.G. Ménache, and F.J. Miller, Toxicol. Appl. Pharmacol., 89 (1987) 429-437.

11 T.R. Gerrity, R.A. Weaver, I. Berntsen, D.E. House, and J.J. O'Neil, J. Appl. Physiol., (1988), in press.

12 J.H. Overton and R.C. Graham, In Program and Abstracts of the 1985 Annual Meeting of the American Associates for Aerosol Research, November 1985, Abstract *9P7, pp. 223.

13 D. Bartlett, C.S. Faulkner, II, and K. Cook, J. Appl. Physiol., 37 (1974) 92-96.

14 N.M. Elsayed, M.G. Mustafa, and E.M. Postlethwait, J. Toxicol. Environ. Health, 9 (1982) 835-848.

15 C.A. Tyson, K.D. Lunan, and R.J. Stephens, Arch. Environ. Health, 37 (1982) 167-176.

16 R.J. Stephens, M.F. Sloan, D.G. Groth, D.G. Negi, and K.D. Lunan, Am. J. Pathol., 93 (1978) 183-200.

17 J. Kagawa and T. Toyama, Arch. Environ. Health, 30 (1975) 117-122.

18 M. Lippmann, P.J. Lioy, G. Leikauf, K.B. Green, D. Baxter, M. Morandi, B.S. Pasterhack, D. Fife, and F.E. Speizer, In Lee et al. (Editors), The Biochemical Effects of Ozone and Related Photochemical Oxidants, Princeton Scientific Publishers, Princeton, 1983, pp.423-446.

19 L.J. Folinsbee, B.L. Drinkwater, J.F. Bedi, and S.M. Horvath, In Folinsbee et al. (Editors), Environmental Stress: Individual Adaptation, Academic Press, New York, 1978, pp. 111-124.

20 W.F. McDonnell, R.S. Chapman, D.H. Horstman, M.W. Leigh, S. Abdul-Salaam, In S.D. Lee (Editor), Evaluation of the Scientific Basis for Ozone/ Oxidants Standards, Air Pollution Control Association, Pittsburgh, 1985, 317-328.

21 J.H. Overton and R.C. Graham, In Proceeding of the 26th Hanford Life Sciences Symposium, Richland, Washington, October 20-23, 1987 (submitted for publication).

22 R.R. Mercer and J.D. Crapo, In Crapo et al. (Editors), Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases, Academic Press, New York, 1988 (submitted for publication).

23 J.H. Overton, A.E. Barnett, and R.C. Graham, In Crapo et al. (Editors), Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases, Academic Press, New York, 1988 (submitted for publication).

24 O.G. Raabe, H.C. Yeh, G.M. Schum, R.F. Phalen, In Tracheobronchial Geometry: Human, Dog, Rat, Hamster, LF-53, Lovelace Foundation, Albuquerque, New Mexico, 1976.